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(FILE 'HOME' ENTERED AT 18:02:24 ON 22 MAR 2006)

FILE 'CAPLUS, MEDLINE' ENTERED AT 18:02:34 ON 22 MAR 2006

| | |
|----|---|
| L1 | 0 S EPOTHILONE? (P) ETHANOL (P) POLYOXYETHYLENE SORBITAN ?OLEATE |
| L2 | 0 S EPOTHILONE? (P) POLYOXYETHYLENE SORBITAN ?OLEATE (P) CYCLODEX |
| L3 | 0 S EPOTHILONE? (P) POLYOXYETHYLENE SORBITAN ?OLEATE |
| L4 | 0 S EPOTHILONE? (P) POLYOXYETHYLENE SORBITAN (P) CYCLODEXTRIN? |
| L5 | 7 S EPOTHILONE? (P) CYCLODEXTRIN? |

L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:549398 CAPLUS

DOCUMENT NUMBER: 131:169392

TITLE: Fermentative preparation process for cytostatics and crystal forms thereof

INVENTOR(S): Hofmann, Hans; Mahnke, Marion; Memmert, Klaus; Petersen, Frank; Schupp, Thomas; Kusters, Ernst; Mutz, Michael

PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.

SOURCE: PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-------------------|----------|
| WO 9942602 | A2 | 19990826 | WO 1999-EP1025 | 19990217 |
| WO 9942602 | A3 | 19991125 | | |
| W: | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW | | | |
| RW: | GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| US 6194181 | B1 | 20010227 | US 1999-248910 | 19990212 |
| CA 2318818 | AA | 19990826 | CA 1999-2318818 | 19990217 |
| AU 9930287 | A1 | 19990906 | AU 1999-30287 | 19990217 |
| AU 746294 | B2 | 20020418 | | |
| BR 9908119 | A | 20001024 | BR 1999-8119 | 19990217 |
| EP 1054994 | A2 | 20001129 | EP 1999-911678 | 19990217 |
| EP 1054994 | B1 | 20041117 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO | | | |
| TR 200002431 | T2 | 20010122 | TR 2000-200002431 | 19990217 |
| JP 2002504346 | T2 | 20020212 | JP 2000-532542 | 19990217 |
| JP 3681109 | B2 | 20050810 | | |
| TR 200101634 | T2 | 20020621 | TR 2001-200101634 | 19990217 |
| NZ 506138 | A | 20030725 | NZ 1999-506138 | 19990217 |
| EP 1428826 | A2 | 20040616 | EP 2004-2632 | 19990217 |
| EP 1428826 | A3 | 20041027 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY | | | |
| CN 1535971 | A | 20041013 | CN 2004-10034240 | 19990217 |
| NZ 525622 | A | 20041029 | NZ 1999-525622 | 19990217 |
| AT 282710 | E | 20041215 | AT 1999-911678 | 19990217 |
| PT 1054994 | T | 20050429 | PT 1999-911678 | 19990217 |
| ES 2233028 | T3 | 20050601 | ES 1999-911678 | 19990217 |
| RU 2268306 | C2 | 20060120 | RU 2000-124168 | 19990217 |
| NO 2000004114 | A | 20001017 | NO 2000-4114 | 20000817 |
| US 6380227 | B1 | 20020430 | US 2000-656954 | 20000907 |
| HK 1034100 | A1 | 20050715 | HK 2001-102978 | 20010425 |
| US 2002165256 | A1 | 20021107 | US 2002-59587 | 20020129 |
| US 6656711 | B2 | 20031202 | | |
| US 2003194787 | A1 | 20031016 | US 2003-338336 | 20030108 |
| US 2003220379 | A1 | 20031127 | US 2003-459762 | 20030612 |
| US 2004142990 | A1 | 20040722 | US 2004-754661 | 20040108 |
| JP 2005068156 | A2 | 20050317 | JP 2004-287797 | 20040930 |
| NO 2005002034 | A | 20001017 | NO 2005-2034 | 20050426 |

PRIORITY APPLN. INFO.:

| | |
|----------------|-------------|
| CH 1998-396 | A 19980219 |
| CH 1998-1007 | A 19980505 |
| US 1999-248910 | A3 19990212 |
| EP 1999-911678 | A3 19990217 |
| JP 2000-532542 | A3 19990217 |
| WO 1999-EP1025 | W 19990217 |
| US 2000-656954 | A1 20000907 |
| US 2002-59587 | A3 20020129 |
| US 2003-338336 | B1 20030108 |

AB The invention relates to a process for concentrating epothilones in culture media, a process for the production of epothilones, a process for separating epothilones A and B and a strain obtained by mutagenesis for the production of epothilones, as well as aspects related thereto. Crystal forms of epothilone B are also described.

ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 1999:549398 CAPLUS
 DOCUMENT NUMBER: 131:169392
 TITLE: Fermentative preparation process for cytostatics and crystal forms thereof
 INVENTOR(S): Hofmann, Hans; Mahnke, Marion; Memmert, Klaus; Petersen, Frank; Schupp, Thomas; Kusters, Ernst; Mutz, Michael
 PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
 SOURCE: PCT Int. Appl., 50 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-------------------|------------|
| WO 9942602 | A2 | 19990826 | WO 1999-EP1025 | 19990217 |
| WO 9942602 | A3 | 19991125 | | |
| W: | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW | | | |
| RW: | GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| US 6194181 | B1 | 20010227 | US 1999-248910 | 19990212 |
| CA 2318818 | AA | 19990826 | CA 1999-2318818 | 19990217 |
| AU 9930287 | A1 | 19990906 | AU 1999-30287 | 19990217 |
| AU 746294 | B2 | 20020418 | | |
| BR 9908119 | A | 20001024 | BR 1999-8119 | 19990217 |
| EP 1054994 | A2 | 20001129 | EP 1999-911678 | 19990217 |
| EP 1054994 | B1 | 20041117 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO | | | |
| TR 200002431 | T2 | 20010122 | TR 2000-200002431 | 19990217 |
| JP 2002504346 | T2 | 20020212 | JP 2000-532542 | 19990217 |
| JP 3681109 | B2 | 20050810 | | |
| TR 200101634 | T2 | 20020621 | TR 2001-200101634 | 19990217 |
| NZ 506138 | A | 20030725 | NZ 1999-506138 | 19990217 |
| EP 1428826 | A2 | 20040616 | EP 2004-2632 | 19990217 |
| EP 1428826 | A3 | 20041027 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY | | | |
| CN 1535971 | A | 20041013 | CN 2004-10034240 | 19990217 |
| NZ 525622 | A | 20041029 | NZ 1999-525622 | 19990217 |
| AT 282710 | E | 20041215 | AT 1999-911678 | 19990217 |
| PT 1054994 | T | 20050429 | PT 1999-911678 | 19990217 |
| ES 2233028 | T3 | 20050601 | ES 1999-911678 | 19990217 |
| RU 2268306 | C2 | 20060120 | RU 2000-124168 | 19990217 |
| NO 2000004114 | A | 20001017 | NO 2000-4114 | 20000817 |
| US 6380227 | B1 | 20020430 | US 2000-656954 | 20000907 |
| HK 1034100 | A1 | 20050715 | HK 2001-102978 | 20010425 |
| US 2002165256 | A1 | 20021107 | US 2002-59587 | 20020129 |
| US 6656711 | B2 | 20031202 | | |
| US 2003194787 | A1 | 20031016 | US 2003-338336 | 20030108 |
| US 2003220379 | A1 | 20031127 | US 2003-459762 | 20030612 |
| US 2004142990 | A1 | 20040722 | US 2004-754661 | 20040108 |
| JP 2005068156 | A2 | 20050317 | JP 2004-287797 | 20040930 |
| NO 2005002034 | A | 20001017 | NO 2005-2034 | 20050426 |
| PRIORITY APPLN. INFO.: | | | CH 1998-396 | A 19980219 |

| | |
|----------------|-------------|
| CH 1998-1007 | A 19980505 |
| US 1999-248910 | A3 19990212 |
| EP 1999-911678 | A3 19990217 |
| JP 2000-532542 | A3 19990217 |
| WO 1999-EP1025 | W 19990217 |
| US 2000-656954 | A1 20000907 |
| US 2002-59587 | A3 20020129 |
| US 2003-338336 | B1 20030108 |

AB The invention relates to a process for concentrating epothilones in culture media, a process for the production of epothilones, a process for separating epothilones A and B and a strain obtained by mutagenesis for the production of epothilones, as well as aspects related thereto. Crystal forms of epothilone B are also described.

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:811346 CAPLUS

DOCUMENT NUMBER: 132:60132

TITLE: Genes for the biosynthesis of epothilones by Sorangium cellulosum

INVENTOR(S): Schupp, Thomas; Ligon, James Madison; Molnar, Istvan; Zirkle, Ross; Gorlach, Jorn; Cyr, Devon

PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft mbH

SOURCE: PCT Int. Appl., 174 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-------------------|-------------|
| WO 9966028 | A2 | 19991223 | WO 1999-EP4171 | 19990616 |
| WO 9966028 | A3 | 20000629 | | |
| W: | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW | | | |
| RW: | GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| NZ 508326 | A | 20031031 | NZ 1998-508326 | 19980612 |
| CA 2329774 | AA | 19991223 | CA 1999-2329774 | 19990616 |
| AU 9946116 | A1 | 20000105 | AU 1999-46116 | 19990616 |
| AU 753567 | B2 | 20021024 | | |
| BR 9911349 | A | 20010313 | BR 1999-11349 | 19990616 |
| EP 1088078 | A2 | 20010404 | EP 1999-929243 | 19990616 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO | | | |
| TR 200003759 | T2 | 20010621 | TR 2000-200003759 | 19990616 |
| JP 2002518004 | T2 | 20020625 | JP 2000-554837 | 19990616 |
| RU 2234532 | C2 | 20040820 | RU 2000-131705 | 19990616 |
| RU 2265054 | C2 | 20051127 | RU 2003-130458 | 19990616 |
| US 6121029 | A | 20000919 | US 1999-335409 | 19990617 |
| US 6346404 | B1 | 20020212 | US 2000-568102 | 20000510 |
| US 6355457 | B1 | 20020312 | US 2000-567969 | 20000510 |
| US 6355458 | B1 | 20020312 | US 2000-568480 | 20000510 |
| US 6355459 | B1 | 20020312 | US 2000-568486 | 20000510 |
| US 6358719 | B1 | 20020319 | US 2000-568472 | 20000510 |
| US 6383787 | B1 | 20020507 | US 2000-567899 | 20000510 |
| ZA 2000007145 | A | 20011022 | ZA 2000-7145 | 20001204 |
| NO 2000006195 | A | 20010216 | NO 2000-6195 | 20001206 |
| US 2002192778 | A1 | 20021219 | US 2001-14717 | 20011113 |
| US 6858404 | B2 | 20050222 | | |
| JP 2006061166 | A2 | 20060309 | JP 2005-305998 | 20051020 |
| PRIORITY APPLN. INFO.: | | | US 1998-155183P | P 19980618 |
| | | | US 1998-99504 | A 19980618 |
| | | | US 1998-101631P | P 19980924 |
| | | | US 1999-118906P | P 19990205 |
| | | | JP 2000-554837 | A3 19990616 |
| | | | RU 2000-131705 | A 19990616 |
| | | | WO 1999-EP4171 | W 19990616 |
| | | | US 1999-335409 | A3 19990617 |
| | | | US 2000-568472 | A1 20000510 |
| AB | Nucleic acid mols. are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone in Sorangium | | | |

cellulosum strain 90 (DSM 6773). The gene cluster includes 22 open reading frames, several of which include domains for a given distinct activity of the epothilone synthase, including acyl carrier protein, β -ketosynthase, acyltransferase, β -ketoreductase, dehydratase, enoyl reductase, and thioesterase. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

L5 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:592097 CAPLUS
 DOCUMENT NUMBER: 143:103272
 TITLE: Therapeutic formulations containing epothilone derivatives
 INVENTOR(S): Sherrill, Michael; Johnson, Robert G.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 12 pp., Cont.-in-part of U.S. Ser. No.683,952.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|-------------|
| US 2005148543 | A1 | 20050707 | US 2004-962308 | 20041008 |
| WO 2004032866 | A2 | 20040422 | WO 2003-US32055 | 20031009 |
| WO 2004032866 | A3 | 20040729 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004132692 | A1 | 20040708 | US 2003-683952 | 20031009 |
| PRIORITY APPLN. INFO.: | | | | |
| | | | US 2003-683952 | A2 20031009 |
| | | | WO 2003-US32055 | A2 20031009 |
| | | | US 2002-417536P | P 20021009 |
| | | | US 2002-426585P | P 20021114 |
| AB Formulations comprising one or more epothilones together with a pharmaceutically acceptable carrier are described. E.g., an epothilone D-hydroxypropyl β-cyclodextrin lyophilizate was prepared for reconstitution for injections. | | | | |

L5 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
 ACCESSION NUMBER: 2005:346870 CAPLUS
 DOCUMENT NUMBER: 142:397752
 TITLE: Therapeutic formulations containing epothilones
 INVENTOR(S): Sherrill, Michael; Johnson, Robert G., Jr.
 PATENT ASSIGNEE(S): Kosan Biosciences, Inc., USA
 SOURCE: PCT Int. Appl., 32 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2005034964 | A1 | 20050421 | WO 2004-US33339 | 20041008 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, | | | | |

AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

WO 2004032866 A2 20040422 WO 2003-US332055 20031009
WO 2004032866 A3 20040729

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004132692 A1 20040708 US 2003-683952 20031009

PRIORITY APPLN. INFO.:

US 2003-683952 A 20031009

WO 2003-US32055 A 20031009

US 2002-417536P P 20021009

US 2002-426585P P 20021114

AB Formulations comprise 1 or more **epothilones** together with a pharmaceutically acceptable carrier. Thus, a combination of 10 mg **epothilone D** and 0.4 g hydroxypropyl-3-**cyclodextrin** were dissolved in 60% tert-butanol-water to make 1 mL of solution. A second solution having 10 mg **epothilone D** and 10 mg mannitol dissolved in 60% tert-butanol-water was prepared. A third solution of 10 mg **epothilone D** and 10 mg mannitol in 60% tert-butanol-water was also prepared. Each of the 3 solns. was freeze-dried to form an excellent cake. The cake containing hydroxypropyl- β - **cyclodextrin** appeared harder and less smooth than the other 2 cakes.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:1066047 CAPLUS

DOCUMENT NUMBER: 142:62404

TITLE: Kinetics and mechanism of degradation of **epothilone-D**: An experimental anticancer agent

AUTHOR(S): Jumaa, M.; Carlson, B.; Chimilio, L.; Silchenko, S.; Stella, V. J.

CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Kansas, Lawrence, KS, 66047, USA

SOURCE: Journal of Pharmaceutical Sciences (2004), 93(12), 2953-2961

CODEN: JPMSAE; ISSN: 0022-3549

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The objective of this study was to investigate the stability and the degradation pathway of **epothilone-D** (Epo-D), an exptl. anticancer agent. In pH range 4-9, Epo-D displayed pH-independent stability and the highest stability was observed at pH 1.5-2 where its thiazole group is protonated. Increasing the pH >9 or <1.5 resulted in an increase in the degradation rate. Epo-D contains an ester group that can be hydrolyzed. The formation of the hydrolytic product was confirmed by the NMR, fast atom bombardment mass spectroscopy, and liquid chromatog./mass spectroscopy/mass spectroscopy techniques. The largely sigmoidal pH-rate profile is not consistent with the normal pH dependency of ester hydrolysis involving an addition/elimination mechanism. Hence, a hydrolysis mechanism through a carbonium ion was suggested. At pH 4 and 7.4, no buffer catalysis was observed (0.01, 0.02, and 0.05 M buffers) and no significant deuterium kinetic solvent isotope effect was noted. The degradation was very sensitive to changes in the dielec. constant of the solvents as significant

enhancement in the stability was observed in buffer-acetonitrile and 0.1 M (SBE)7m- β - **cyclodextrin** solns. compared with just buffer, suggesting that the rate-determining step in the degradation pathway involved formation of a polar transition state. Mass spectral anal. of the reaction run in 180 water was consistent with incorporation of the 180 in the alc. hydroxyl rather than the carboxylate group. These observations strongly support the carbonium ion mechanism for the hydrolysis of Epo-D in the pH range 4-9. A pKa value of 2.86 for Epo-D was estimated from the fit of the pH-rate profile. This number was confirmed independently by the changes in UV absorbance of Epo-D as a function of pH (pKa 3.1) determined at 25°C and the same ionic strength.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:331933 CAPLUS

DOCUMENT NUMBER: 140:344910

TITLE: Therapeutic formulations containing epothilones for treatment of hyperproliferative diseases

INVENTOR(S): Sherrill, Michael; Johnson, Robert G.

PATENT ASSIGNEE(S): Kosan Biosciences, Inc., USA

SOURCE: PCT Int. Appl., 22 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|--|------------|
| WO 2004032866 | A2 | 20040422 | WO 2003-US32055 | 20031009 |
| WO 2004032866 | A3 | 20040729 | | |
| W: | | | | |
| AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: | | | | |
| GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1551425 | A2 | 20050713 | EP 2003-773227 | 20031009 |
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| AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| JP 2006504743 | T2 | 20060209 | JP 2004-543618 | 20031009 |
| WO 2005034964 | A1 | 20050421 | WO 2004-US33339 | 20041008 |
| W: | | | | |
| AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
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| BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2005148543 | A1 | 20050707 | US 2004-962308 | 20041008 |
| PRIORITY APPLN. INFO.: | | | US 2002-417536P | P 20021009 |
| | | | US 2002-426585P | P 20021114 |
| | | | US 2003-683952 | A 20031009 |
| | | | WO 2003-US32055 | W 20031009 |
| AB | | | Formulations comprising one or more epothilones together with a | |

pharmaceutically acceptable carrier, in particular such pharmaceutical compns. suitable for oral administration of an **epothilone** are described. For example, a combination of 10 mg of **epothilone D** and 0.4 g of hydroxypropyl- β - **cyclodextrin** were dissolved in 60% tert-butanol-water to make 1 mL of solution. The solution was freeze-dried and formed an excellent lyophilate cake. The cake appeared harder and less smooth than the one containing mannitol. The **epothilone D** formulation had good oral bioavailability, suggesting that oral administration to cancer patients or patients suffering from other hyperproliferative conditions or diseases is feasible.

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:811346 CAPLUS
DOCUMENT NUMBER: 132:60132
TITLE: Genes for the biosynthesis of epothilones by *Sorangium cellulosum*
INVENTOR(S): Schupp, Thomas; Ligon, James Madison; Molnar, Istvan; Zirkle, Ross; Gorlach, Jorn; Cyr, Devon
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft mbH
SOURCE: PCT Int. Appl., 174 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-------------------|------------|
| WO 9966028 | A2 | 19991223 | WO 1999-EP4171 | 19990616 |
| WO 9966028 | A3 | 20000629 | | |
| W: | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW | | | |
| RW: | GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| NZ 508326 | A | 20031031 | NZ 1998-508326 | 19980612 |
| CA 2329774 | AA | 19991223 | CA 1999-2329774 | 19990616 |
| AU 9946116 | A1 | 20000105 | AU 1999-46116 | 19990616 |
| AU 753567 | B2 | 20021024 | | |
| BR 9911349 | A | 20010313 | BR 1999-11349 | 19990616 |
| EP 1088078 | A2 | 20010404 | EP 1999-929243 | 19990616 |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO | | | |
| TR 200003759 | T2 | 20010621 | TR 2000-200003759 | 19990616 |
| JP 2002518004 | T2 | 20020625 | JP 2000-554837 | 19990616 |
| RU 2234532 | C2 | 20040820 | RU 2000-131705 | 19990616 |
| RU 2265054 | C2 | 20051127 | RU 2003-130458 | 19990616 |
| US 6121029 | A | 20000919 | US 1999-335409 | 19990617 |
| US 6346404 | B1 | 20020212 | US 2000-568102 | 20000510 |
| US 6355457 | B1 | 20020312 | US 2000-567969 | 20000510 |
| US 6355458 | B1 | 20020312 | US 2000-568480 | 20000510 |
| US 6355459 | B1 | 20020312 | US 2000-568486 | 20000510 |
| US 6358719 | B1 | 20020319 | US 2000-568472 | 20000510 |
| US 6383787 | B1 | 20020507 | US 2000-567899 | 20000510 |
| ZA 2000007145 | A | 20011022 | ZA 2000-7145 | 20001204 |
| NO 2000006195 | A | 20010216 | NO 2000-6195 | 20001206 |
| US 2002192778 | A1 | 20021219 | US 2001-14717 | 20011113 |
| US 6858404 | B2 | 20050222 | | |
| JP 2006061166 | A2 | 20060309 | JP 2005-305998 | 20051020 |
| PRIORITY APPLN. INFO.: | | | US 1998-155183P | P 19980618 |

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|-----------------|----|----------|
| US 1998-99504 | A | 19980618 |
| US 1998-101631P | P | 19980924 |
| US 1999-118906P | P | 19990205 |
| JP 2000-554837 | A3 | 19990616 |
| RU 2000-131705 | A | 19990616 |
| WO 1999-EP4171 | W | 19990616 |
| US 1999-335409 | A3 | 19990617 |
| US 2000-568472 | A1 | 20000510 |

AB Nucleic acid mols. are isolated from Sorangium cellulosum that encode polypeptides necessary for the biosynthesis of epothilone in Sorangium cellulosum strain 90 (DSM 6773). The gene cluster includes 22 open reading frames, several of which include domains for a given distinct activity of the epothilone synthase, including acyl carrier protein, β -ketosynthase, acyltransferase, β -ketoreductase, dehydratase, enoyl reductase, and thioesterase. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:549398 CAPLUS
DOCUMENT NUMBER: 131:169392
TITLE: Fermentative preparation process for cytostatics and crystal forms thereof
INVENTOR(S): Hofmann, Hans; Mahnke, Marion; Memmert, Klaus; Petersen, Frank; Schupp, Thomas; Kusters, Ernst; Mutz, Michael
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 9942602 | A2 | 19990826 | WO 1999-EP1025 | 19990217 |
| WO 9942602 | A3 | 19991125 | | |
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| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 6194181 | B1 | 20010227 | US 1999-248910 | 19990212 |
| CA 2318818 | AA | 19990826 | CA 1999-2318818 | 19990217 |
| AU 9930287 | A1 | 19990906 | AU 1999-30287 | 19990217 |
| AU 746294 | B2 | 20020418 | | |
| BR 9908119 | A | 20001024 | BR 1999-8119 | 19990217 |
| EP 1054994 | A2 | 20001129 | EP 1999-911678 | 19990217 |
| EP 1054994 | B1 | 20041117 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO | | | | |
| TR 200002431 | T2 | 20010122 | TR 2000-200002431 | 19990217 |
| JP 2002504346 | T2 | 20020212 | JP 2000-532542 | 19990217 |
| JP 3681109 | B2 | 20050810 | | |
| TR 200101634 | T2 | 20020621 | TR 2001-200101634 | 19990217 |
| NZ 506138 | A | 20030725 | NZ 1999-506138 | 19990217 |
| EP 1428826 | A2 | 20040616 | EP 2004-2632 | 19990217 |

EP 1428826 A3 20041027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI, CY

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|---------------|----|----------|------------------|----------|
| CN 1535971 | A | 20041013 | CN 2004-10034240 | 19990217 |
| NZ 525622 | A | 20041029 | NZ 1999-525622 | 19990217 |
| AT 282710 | E | 20041215 | AT 1999-911678 | 19990217 |
| PT 1054994 | T | 20050429 | PT 1999-911678 | 19990217 |
| ES 2233028 | T3 | 20050601 | ES 1999-911678 | 19990217 |
| RU 2268306 | C2 | 20060120 | RU 2000-124168 | 19990217 |
| NO 2000004114 | A | 20001017 | NO 2000-4114 | 20000817 |
| US 6380227 | B1 | 20020430 | US 2000-656954 | 20000907 |
| HK 1034100 | A1 | 20050715 | HK 2001-102978 | 20010425 |
| US 2002165256 | A1 | 20021107 | US 2002-59587 | 20020129 |
| US 6656711 | B2 | 20031202 | | |
| US 2003194787 | A1 | 20031016 | US 2003-338336 | 20030108 |
| US 2003220379 | A1 | 20031127 | US 2003-459762 | 20030612 |
| US 2004142990 | A1 | 20040722 | US 2004-754661 | 20040108 |
| JP 2005068156 | A2 | 20050317 | JP 2004-287797 | 20040930 |
| NO 2005002034 | A | 20001017 | NO 2005-2034 | 20050426 |

PRIORITY APPLN. INFO.:

| | | |
|----------------|----|----------|
| CH 1998-396 | A | 19980219 |
| CH 1998-1007 | A | 19980505 |
| US 1999-248910 | A3 | 19990212 |
| EP 1999-911678 | A3 | 19990217 |
| JP 2000-532542 | A3 | 19990217 |
| WO 1999-EP1025 | W | 19990217 |
| US 2000-656954 | A1 | 20000907 |
| US 2002-59587 | A3 | 20020129 |
| US 2003-338336 | B1 | 20030108 |

AB The invention relates to a process for concentrating epothilones in culture media, a process for the production of epothilones, a process for separating epothilones A and B and a strain obtained by mutagenesis for the production of epothilones, as well as aspects related thereto. Crystal forms of epothilone B are also described.

L5 ANSWER 7 OF 7 MEDLINE on STN

ACCESSION NUMBER: 2004551316 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15459947

TITLE: Kinetics and mechanism of degradation of epothilone-D: an experimental anticancer agent.

AUTHOR: Jumaa M; Carlson B; Chimilio L; Silchenko S; Stella V J

CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of Kansas, 2095 Constant Avenue, Lawrence, Kansas 66047, USA.

CONTRACT NUMBER: N01-CM-77017 (NCI)

N01-CM27004 (NCI)

SOURCE: Journal of pharmaceutical sciences, (2004 Dec) Vol. 93, No. 12, pp. 2953-61.

Journal code: 2985195R. ISSN: 0022-3549.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200504

ENTRY DATE: Entered STN: 20041104

Last Updated on STN: 20050413

Entered Medline: 20050412

AB The objective of this study was to investigate the stability and the degradation pathway of epothilone-D (Epo-D), an experimental anticancer agent. In pH range 4-9, Epo-D displayed pH-independent stability and the highest stability was observed at pH 1.5-2 where its thiazole group is protonated. Increasing the pH >9 or <1.5 resulted in an increase in the degradation rate. Epo-D contains an ester group that can be hydrolyzed. The formation of the hydrolytic product was confirmed by the nuclear magnetic resonance (NMR), fast atom bombardment mass spectroscopy and liquid chromatography/mass spectroscopy/mass spectroscopy

techniques. The largely sigmoidal pH-rate profile is not consistent with the normal pH dependency of ester hydrolysis involving an addition/elimination mechanism. Hence, a hydrolysis mechanism through a carbonium ion was suggested. At pH 4 and 7.4, no buffer catalysis was observed (0.01, 0.02, and 0.05 M buffers) and no significant deuterium kinetic solvent isotope effect was noted. The degradation was very sensitive to changes in the dielectric constant of the solvents as significant enhancement in the stability was observed in buffer-acetonitrile and 0.1 M (SBE)7m-beta-cyclodextrin solutions compared with just buffer, suggesting that the rate-determining step in the degradation pathway involved formation of a polar transition state. Mass spectral analysis of the reaction run in 18O water was consistent with incorporation of the 18O in the alcohol hydroxyl rather than the carboxylate group. These observations strongly support the carbonium ion mechanism for the hydrolysis of Epo-D in the pH range 4-9. A pKa value of 2.86 for Epo-D was estimated from the fit of the pH-rate profile. This number was confirmed independently by the changes in ultraviolet absorbance of Epo-D as a function of pH (pKa 3.1) determined at 25 degrees C and the same ionic strength.

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(FILE 'HOME' ENTERED AT 18:02:24 ON 22 MAR 2006)

FILE 'CAPLUS, MEDLINE' ENTERED AT 18:02:34 ON 22 MAR 2006

| | |
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| L1 | 0 S EPOTHILONE? (P) ETHANOL (P) POLYOXYETHYLENE SORBITAN ?OLEATE |
| L2 | 0 S EPOTHILONE? (P) POLYOXYETHYLENE SORBITAN ?OLEATE (P) CYCLODEX |
| L3 | 0 S EPOTHILONE? (P) POLYOXYETHYLENE SORBITAN ?OLEATE |
| L4 | 0 S EPOTHILONE? (P) POLYOXYETHYLENE SORBITAN (P) CYCLODEXTRIN? |
| L5 | 7 S EPOTHILONE? (P) CYCLODEXTRIN? |

L5 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:549398 CAPLUS

DOCUMENT NUMBER: 131:169392

TITLE: Fermentative preparation process for cytostatics and crystal forms thereof

INVENTOR(S): Hofmann, Hans; Mahnke, Marion; Memmert, Klaus; Petersen, Frank; Schupp, Thomas; Kusters, Ernst; Mutz, Michael

PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.

SOURCE: PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-------------------|----------|
| WO 9942602 | A2 | 19990826 | WO 1999-EP1025 | 19990217 |
| WO 9942602 | A3 | 19991125 | | |
| W: | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW | | | |
| RW: | GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | |
| US 6194181 | B1 | 20010227 | US 1999-248910 | 19990212 |
| CA 2318818 | AA | 19990826 | CA 1999-2318818 | 19990217 |
| AU 9930287 | A1 | 19990906 | AU 1999-30287 | 19990217 |
| AU 746294 | B2 | 20020418 | | |
| BR 9908119 | A | 20001024 | BR 1999-8119 | 19990217 |
| EP 1054994 | A2 | 20001129 | EP 1999-911678 | 19990217 |
| EP 1054994 | B1 | 20041117 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO | | | |
| TR 200002431 | T2 | 20010122 | TR 2000-200002431 | 19990217 |
| JP 2002504346 | T2 | 20020212 | JP 2000-532542 | 19990217 |
| JP 3681109 | B2 | 20050810 | | |
| TR 200101634 | T2 | 20020621 | TR 2001-200101634 | 19990217 |
| NZ 506138 | A | 20030725 | NZ 1999-506138 | 19990217 |
| EP 1428826 | A2 | 20040616 | EP 2004-2632 | 19990217 |
| EP 1428826 | A3 | 20041027 | | |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY | | | |
| CN 1535971 | A | 20041013 | CN 2004-10034240 | 19990217 |
| NZ 525622 | A | 20041029 | NZ 1999-525622 | 19990217 |
| AT 282710 | E | 20041215 | AT 1999-911678 | 19990217 |
| PT 1054994 | T | 20050429 | PT 1999-911678 | 19990217 |
| ES 2233028 | T3 | 20050601 | ES 1999-911678 | 19990217 |
| RU 2268306 | C2 | 20060120 | RU 2000-124168 | 19990217 |
| NO 2000004114 | A | 20001017 | NO 2000-4114 | 20000817 |
| US 6380227 | B1 | 20020430 | US 2000-656954 | 20000907 |
| HK 1034100 | A1 | 20050715 | HK 2001-102978 | 20010425 |
| US 2002165256 | A1 | 20021107 | US 2002-59587 | 20020129 |
| US 6656711 | B2 | 20031202 | | |
| US 2003194787 | A1 | 20031016 | US 2003-338336 | 20030108 |
| US 2003220379 | A1 | 20031127 | US 2003-459762 | 20030612 |
| US 2004142990 | A1 | 20040722 | US 2004-754661 | 20040108 |
| JP 2005068156 | A2 | 20050317 | JP 2004-287797 | 20040930 |
| NO 2005002034 | A | 20001017 | NO 2005-2034 | 20050426 |

PRIORITY APPLN. INFO.:

| | |
|----------------|-------------|
| CH 1998-396 | A 19980219 |
| CH 1998-1007 | A 19980505 |
| US 1999-248910 | A3 19990212 |
| EP 1999-911678 | A3 19990217 |
| JP 2000-532542 | A3 19990217 |
| WO 1999-EP1025 | W 19990217 |
| US 2000-656954 | A1 20000907 |
| US 2002-59587 | A3 20020129 |
| US 2003-338336 | B1 20030108 |

AB The invention relates to a process for concentrating epothilones in culture media, a process for the production of epothilones, a process for separating epothilones A and B and a strain obtained by mutagenesis for the production of epothilones, as well as aspects related thereto. Crystal forms of epothilone B are also described.

L5 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:811346 CAPLUS

DOCUMENT NUMBER: 132:60132

TITLE: Genes for the biosynthesis of epothilones by Sorangium cellulosum

INVENTOR(S): Schupp, Thomas; Ligon, James Madison; Molnar, Istvan; Zirkle, Ross; Gorlach, Jorn; Cyr, Devon

PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft mbH

SOURCE: PCT Int. Appl., 174 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-------------------|-------------|
| WO 9966028 | A2 | 19991223 | WO 1999-EP4171 | 19990616 |
| WO 9966028 | A3 | 20000629 | | |
| W: | | | | |
| AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, | | | | |
| DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, | | | | |
| JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, | | | | |
| MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, | | | | |
| TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: | | | | |
| GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, | | | | |
| ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, | | | | |
| CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| NZ 508326 | A | 20031031 | NZ 1998-508326 | 19980612 |
| CA 2329774 | AA | 19991223 | CA 1999-2329774 | 19990616 |
| AU 9946116 | A1 | 20000105 | AU 1999-46116 | 19990616 |
| AU 753567 | B2 | 20021024 | | |
| BR 9911349 | A | 20010313 | BR 1999-11349 | 19990616 |
| EP 1088078 | A2 | 20010404 | EP 1999-929243 | 19990616 |
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| AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, | | | | |
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| TR 200003759 | T2 | 20010621 | TR 2000-200003759 | 19990616 |
| JP 2002518004 | T2 | 20020625 | JP 2000-554837 | 19990616 |
| RU 2234532 | C2 | 20040820 | RU 2000-131705 | 19990616 |
| RU 2265054 | C2 | 20051127 | RU 2003-130458 | 19990616 |
| US 6121029 | A | 20000919 | US 1999-335409 | 19990617 |
| US 6346404 | B1 | 20020212 | US 2000-568102 | 20000510 |
| US 6355457 | B1 | 20020312 | US 2000-567969 | 20000510 |
| US 6355458 | B1 | 20020312 | US 2000-568480 | 20000510 |
| US 6355459 | B1 | 20020312 | US 2000-568486 | 20000510 |
| US 6358719 | B1 | 20020319 | US 2000-568472 | 20000510 |
| US 6383787 | B1 | 20020507 | US 2000-567899 | 20000510 |
| ZA 2000007145 | A | 20011022 | ZA 2000-7145 | 20001204 |
| NO 2000006195 | A | 20010216 | NO 2000-6195 | 20001206 |
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| US 6858404 | B2 | 20050222 | | |
| JP 2006061166 | A2 | 20060309 | JP 2005-305998 | 20051020 |
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| | | | US 1998-101631P | P 19980924 |
| | | | US 1999-118906P | P 19990205 |
| | | | JP 2000-554837 | A3 19990616 |
| | | | RU 2000-131705 | A 19990616 |
| | | | WO 1999-EP4171 | W 19990616 |
| | | | US 1999-335409 | A3 19990617 |
| | | | US 2000-568472 | A1 20000510 |
| AB | | | | |
| Nucleic acid mols. are isolated from Sorangium cellulosum that encode | | | | |
| polypeptides necessary for the biosynthesis of epothilone in Sorangium | | | | |

cellulosum strain 90 (DSM 6773). The gene cluster includes 22 open reading frames, several of which include domains for a given distinct activity of the epothilone synthase, including acyl carrier protein, β -ketosynthase, acyltransferase, β -ketoreductase, dehydratase, enoyl reductase, and thioesterase. Disclosed are methods for the production of epothilone in recombinant hosts transformed with the genes of the invention. In this manner, epothilone can be produced in quantities large enough to enable their purification and use in pharmaceutical formulations such as those for the treatment of cancer.

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FILE 'CAPLUS, MEDLINE' ENTERED AT 18:02:34 ON 22 MAR 2006

| | | | | | | | | | |
|----|---|---|-------------|-----|-----------------|----------|-----------------|---------------|----------|
| L1 | 0 | S | EPOTHILONE? | (P) | ETHANOL | (P) | POLYOXYETHYLENE | SORBITAN | ?OLEATE |
| L2 | 0 | S | EPOTHILONE? | (P) | POLYOXYETHYLENE | SORBITAN | ?OLEATE | (P) | CYCLODEX |
| L3 | 0 | S | EPOTHILONE? | (P) | POLYOXYETHYLENE | SORBITAN | ?OLEATE | | |
| L4 | 0 | S | EPOTHILONE? | (P) | POLYOXYETHYLENE | SORBITAN | (P) | CYCLODEXTRIN? | |
| L5 | 7 | S | EPOTHILONE? | (P) | CYCLODEXTRIN? | | | | |